Summary: The authors reviewed retrospective cases of 2 women — one aged 78 years and the other aged 86 years — with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer treated with combination palbociclib/letrozole who presented with hyperuricemia. In both cases, the patients experienced hyperuricemia and neutropenia that required palbociclib to be temporarily discontinued and its dose to be subsequently reduced. Although study data have demonstrated that combination palbociclib/letrozole is safe and effective as a first-line treatment option for patients with advanced ER-positive, HER2-negative breast cancer, the efficacy and safety of cyclin-dependent kinase inhibitors, including their adverse events, still remains an active area of research. The authors postulate that hyperuricemia may be a potential adverse event of palbociclib not yet reported in randomized control studies or in clinical practice.

Background
Palbociclib is a selective inhibitor of cyclin-dependent kinases (CDK) 4 and 6 approved as treatment for women with advanced or metastatic estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with manageable adverse events. Data indicate that palbociclib improved the response rate and duration in postmenopausal women with locally advanced or metastatic ER-positive/HER2-negative breast cancer.1 Thus, targeting CDK4/6 may overcome acquired resistance to conventional endocrine therapy. Randomized phase 2 and 3 studies have demonstrated that palbociclib/letrozole as a first-line treatment option for patients with advanced ER-positive, HER2-negative breast cancer is safe and effective, and those data enabled palbociclib to receive expedited approval from the US Food and Drug Administration.2 However, the efficacy and safety of CDK inhibitors, including their adverse events, still remains an active area of research.3

Case Reports
Case 1
A woman aged 78 years presented with lethargy and dehydration. Her chemistry panel revealed hyperuricemia (uric acid, 11.4 mg/dL), hypercalcemia (corrected calcium, 10.9 mg/dL), and acute kidney injury (serum creatinine, 1.5 mg/dL). Seven days prior to this presentation, she had received treatment with letrozole and palbociclib for hormone-receptor (HR)-positive breast cancer metastatic to the bones and bone marrow.

Her past medical history was positive for stage 3 papillary thyroid cancer for which she underwent total thyroidectomy and radioactive iodide therapy. Four years prior to this presentation, she was diagnosed with ER-positive, HER2-negative stage 2 invasive ductal breast cancer for which she underwent partial mastectomy and a single fraction of intraoperative radiation. She was briefly treated with exemestane, but it was stopped due to severe arthralgia, a drug-related adverse event.

Four years after the initial diagnosis of breast cancer, she presented with pancytopenia. Position emission tomography (PET) was obtained that revealed diffuse bone metastases. Subsequent bone marrow biopsy was obtained and the results were consistent with ER/PR-positive, HER2-negative metastatic breast adenocarcinoma involving 60% of the hypercellular bone marrow.

During a 2-day hospitalization, she was treated with aggressive intravenous fluids and allopurinol 300 mg daily. Complete resolution of the acute kidney injury was achieved and her uric acid level was normalized to 3.8 mg/dL. On discharge, she was continued on letrozole, but palbociclib was held for 14 days due to neutropenia. After the neutropenia resolved, her dose of palbociclib was restarted and reduced to 100 mg, and no evidence of recurrent hyperuricemia was seen on treatment day 21. She tolerated this new dose, and, at 8 weeks after the treatment was initiated, her cancer antigen (CA) 15-3 level had declined from 500 to 11 U/mL.
Case 2
A woman aged 86 years presented with a past medical history of right-sided, ER-positive, HER2-negative invasive ductal breast carcinoma. Biopsy was performed and the results confirmed metastasis to the liver. Her right adrenal gland was initially treated with lumpectomy, postoperative radiation, and paclitaxel.

Over the course of 8 years, the adrenal mass and all of the liver masses decreased in size; however, due to a slow increase in CA 15-3 level, she was treated with exemestane and fulvestrant and underwent 2 hepatic artery chemoembolizations. Within 6 months of therapy, results on PET revealed new and increasing liver lesions. Exemestane and fulvestrant were discontinued and palbociclib 125 mg daily and letrozole 2.5 mg daily were started. She developed hyperuricemia within 10 days after therapy was initiated and had a uric acid level of 9.3 mg/dL. Allopurinol 300 mg daily was started and she was instructed to increase her oral fluid intake.

A repeat uric acid test on day 25 of treatment showed a decreased level of 3.6 mg/dL, but palbociclib was held due to neutropenia. After the neutropenia resolved, she was restarted on a reduced dose of palbociclib at 100 mg daily. She completed a total treatment course of 28 days. Her CA 15-3 level declined from 142 U/mL to 86 U/mL.

Discussion
To our knowledge, this is the first time that hyperuricemia has been reported as a possible complication of palbociclib treatment in combination with letrozole since palbociclib was approved by the US Food and Drug Administration. Given the rapid tumor response in the first case, it is reasonable to postulate that hyperuricemia could have resulted from rapid tumor lysis, as confirmed by the rapid decline in tumor marker level.

The safety and efficacy of palbociclib in combination with letrozole as a first-line treatment for patients with advanced ER-positive, HER2-negative breast cancer was demonstrated in a randomized phase 2 study.1 Neutropenia, leukopenia, and fatigue were the most common adverse events.1 In addition, a double-blind, randomized phase 3 trial compared fulvestrant and palbociclib with fulvestrant and placebo for the treatment of metastatic, hormone-responsive breast cancer.4 Results of that phase 3 study revealed that fulvestrant/palbociclib increased the rate of progression-free survival among women with ER-positive, HER2-negative cancer, irrespective of menopausal status.4 In that trial, the most common adverse events were neutropenia, leukopenia, fatigue, and nausea.4 However, the study was stopped early because it met its primary end point of demonstrating an improvement in the rate of progression-free survival.4 Clinically significant hyperuricemia was not noted in either study.1,4

Aromatase inhibitors such as letrozole have an active role in the treatment of ER-positive, postmenopausal breast cancer.3 However, because 30% to 50% of patients do not respond to aromatase inhibitors, ongoing research suggests that more individualized treatment should be developed.3 IL6ST, NGFRAP1, MCM4, and ASPM have been analyzed in patients with postmenopausal, ER-positive invasive breast cancer to attempt to identify biomarkers that can predict which patients may respond better to treatment.3 A treatment model using these genes had rates of accuracy, sensitivity, and specificity of 96%, 96%, and 94%, respectively, for predicting clinical response when high expression of the immune-related genes IL6ST and NGFRAP1 is present prior to treatment and a low expression of the proliferative-associated genes MCM4 and ASPM 2 weeks after letrozole therapy is initiated.3 It may be possible that this same 4-gene signature used for predicting clinical responsiveness to aromatase inhibitors in patients with ER-positive breast cancer could also be used to identify patients at higher risk for hyperuricemia when being treated with palbociclib.

Conclusion
In the absence of a biomarker or other tests to identify those at higher risk for developing hyperuricemia with palbociclib and aromatase inhibitor treatment, the findings of these 2 cases suggest that close monitoring of uric acid levels might be prudent in patients with a high-disease burden who are receiving palbociclib. In patients who develop clinically significant hyperuricemia, reducing the palbociclib dose may be necessary and allopurinol treatment should be timely instituted.

References